RARE DISEASES CLINICAL RESEARCH NETWORK

RELEASE DATE: February 27, 2003

RFA: RR-03-008

National Center for Research Resources (NCRR)
(http://www.ncrr.nih.gov/)
Office of Rare Diseases, NIH (ORD, NIH)
(http://rarediseases.info.nih.gov/)
National Institute of Neurological Disorders and Stroke (NINDS)
(http://www.ninds.nih.gov/)
National Institute of Child Health and Human Development (NICHD)
(http://www.nichd.nih.gov/)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.niams.nih.gov/)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
(http://www.niddk.nih.gov/)

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: 93.389

LETTER OF INTENT RECEIPT DATE: April 1, 2003

APPLICATION RECEIPT DATE: April 29, 2003

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

The National Center for Research Resources (NCRR) the Office of Rare Diseases, National Institutes of Health (ORD, NIH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Child Health and Human Development (NICHD) invite applications for Rare Diseases Clinical Research Centers (RDCRCs) and a Data and Technology Coordinating Center (DTCC), which together will form the Rare Diseases Clinical Research Network.

The purpose of this cooperative research network is to facilitate clinical research in rare diseases through support for 1) collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, phase one and two trials, and/or pilot and demonstration projects; 2) training of clinical investigators in rare diseases research; 3) a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms; and 4) access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public.

Each RDCRC must include a consortium of clinical investigators, institutions, GCRCs, and relevant organizations, including patient support organizations, for the study of a subgroup of rare diseases. The DTCC, a collaboration between data base and computational/computer science innovators, will provide a scalable coordinated clinical data management system for collection, storage, and analysis of data of RDCRCs, a portal and tools for integration of developed and publicly available datasets for data mining at RDCRCs, web based recruitment and referral, and a user friendly resource site for the public, research scientists, and clinicians. This cooperative program should facilitate identification of biomarkers for disease risk, disease severity/activity, and clinical outcome and encourage development of new approaches to diagnosis, prevention, and treatment of rare diseases.

RESEARCH OBJECTIVES

Background

Approximately 25 million people in the United States are affected by an estimated 6,000 rare diseases or conditions leading to significant morbidity and mortality. 'Rare disease' is defined through an Amendment to the Orphan Drug Act of 1983 (Orphan Drug Act, P.L. 97-414; Health Promotion and Disease Prevention Amendments, P.L. 98-551) as a condition affecting fewer than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the drug in the United States.

An NIH ORD Special Emphasis Panel, composed of academic scientists, representatives of voluntary patient support groups, pharmaceutical, biotechnology and device industries, and other Federal agencies, made recommendations on the special research and health care issues posed by rare diseases. These recommendations encompassed four major areas: 1) Stimulating Research on Rare Diseases and Conditions, with specific emphasis on clinical research and training of clinical research scientists, establishing diagnostic and treatment centers with informatics support, and promoting the collaboration of the voluntary patient support groups, health care systems, and industry; 2) Utilizing Research Resources, with the NIH supported GCRCs, the development of a centralized information database containing research resources, made available to research investigators, physicians, and patients for their use; 3) Coordination of Rare Diseases Research and Development Activities, with a primary responsibility of ORD to coordinate activities and act as a liaison between the rare diseases community and the NIH, including the public, and intramural and extramural investigators at the NIH ICs and other Federal agencies, manufacturers, and voluntary organizations; and 4) Identifying Emerging Opportunities in Rare Diseases Research, specifically through the establishment of specialized research and diagnostic centers to attract the interests of industry to promote advances and products for the prevention, diagnosis, and treatment of rare diseases. These recommendations are contained within the Department of Health and Human Services National Institute of Health Report on Steps to Coordinate Rare Diseases Research Programs," January 2001 (http://rarediseases.info.nih.gov/news-reports/reports.html).

In November 2002, the Rare Disease Act of 2002 (Public Law 107-280) directed ORD, NIH to support regional centers of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases. This law provides the legislated mandate for this solicitation to address the needs of rare disease clinical research.

Rare diseases offer promising leads for scientific advancement. Many rare diseases represent single gene defects whose abnormalities in specific genes or proteins offer insight into normal biologic function. Other rare diseases are complex resulting from the interaction of two or more genes. Understanding the pathogenesis of rare diseases may advance our understanding of more common medical disorders.

Despite the advances and opportunities for research in rare diseases, there remain difficulties in clinical diagnosis and management. Diagnosis may be straightforward with well-described phenotypes or difficult with poorly defined criteria. There is insufficient characterization of the course of many rare diseases. Treatment can be equally challenging with many questions concerning appropriate and best clinical management. Rare diseases pose unique challenges to identification and coordination of resources and expertise for small populations dispersed over wide geographic areas. Rare diseases research requires collaboration of scientists from multiple disciplines sharing research resources and patient populations.

Rigorous characterization and longitudinal assessment is needed to facilitate discovery of biomarkers of disease risk, disease activity, and response to therapy. In addition, controversies concerning current treatment strategies could be resolved by systematic assessment. Well described patient populations will be important to bring promising therapies to the clinic.

This initiative will establish a collaborative and coordinated network of investigators and patient groups committed to investigation of rare diseases working in partnership with leaders in technology to enhance communication and sharing of resources in a multidisciplinary approach.

The Rare Diseases Clinical Research Network will focus on the collection of clinical information to develop biomarkers and new approaches to diagnosis, prevention, and treatment and promote the training of new clinical investigators in rare diseases research. The Network will support a comprehensive and integrated approach to data collection, storage, and management, and the integration of clinical data with other unique data, including genetic, imaging, pathologic, laboratory.

The Data and Technology Coordinating Center will incorporate new approaches to distributed computing and federated databases.

Organization of the Rare Diseases Clinical Research Network

The Rare Diseases Clinical Research Network is a cooperative network composed of several Rare Diseases Clinical Research Centers (RDCRCs) and a single Data and Technology Coordinating Center (DTCC) to facilitate clinical research in rare diseases. A Steering Committee, composed at a minimum of the Director of each RDCRC, the Director of the DTCC, the Office of Rare Diseases Program Coordinator, and the NCRR Program Coordinator will establish the procedures for the function of the RDCR Network, as outlined in section "Steering Committee." An independent Scientific Advisory Board (SAB), established by the NIH, will provide independent oversight of the network and each component.

Rare Disease Clinical Research Centers. Each RDCRC will perform collaborative clinical research in rare diseases, train new investigators in rare diseases research, and provide content for an internet resource site on rare diseases. Each RDCRC will consist of a consortium of clinical investigators, institutions, and relevant organizations, including patient support organizations, focused on a subgroup of rare diseases. Use of the resources available at General Clinical Research Centers must be incorporated into each RDCRC. The focus of each Center can be on particular defects, i.e., lysosomal storage diseases, amino acid metabolism defects; particular organ systems, i.e., primary immune deficiencies, mental retardation syndromes; or other groupings. Since rare diseases are diverse, the nature of clinical research that is feasible varies. The application must describe the group of rare diseases to be included, the rationale for this grouping, and the relevant expertise available in the consortium Center.

Each application must include:

- a description and rationale for the planned clinical studies and longitudinal assessment of subjects. Strategies for recruitment, retention, assessment, and analysis must be included. Depending on the state of knowledge of the particular diseases, the clinical studies could include strategies for assessing current therapeutic interventions, phase 1 or 2 clinical trials, or pilot and demonstration projects. Examples of demonstration/pilot studies include development of novel laboratory assays and clinical instruments.

- a plan for training of new investigator(s) for clinical research in rare diseases within their consortium.

- a description of resources to be included in a web site for education and research in rare diseases. These resources should include links or materials for lay public, patients, basic and clinical researchers, and clinicians. Examples include but are not limited to: contacts for animal models; tissue, serum, specimens, DNA, etc; antibodies and research reagents; genetic resources; registries; education materials; and/or diagnostic flow charts. The actual design and implementation of the site will be a collaborative activity of the DTCC and all the RDCRCs through the teering Committee (see below). The Center must agree to work cooperatively to develop the web site resource and provide content related to its focused rare diseases.

The Data and Technology Coordinating Center (DTCC). The Data and Technology Coordinating Center will develop and make available a secure, customizable coordinated clinical data management system for collection, storage, and analysis of diverse data types from multiple diseases and geographically disparate locations. The DTCC should develop and provide a user friendly system for web based recruitment and referral, tools for cross disease data mining, and a portal for access and integration of publicly available data resources. The DTCC should have computational sophistication for scaling the systems and tools to allow incorporation into a distributed, national clinical information network.

The DTCC must address privacy and confidentiality issues related to database management and distributed computing and allow multiple levels of data sharing. The Steering Committee will provide scientific and technical assistance and guidelines with respect to quality control, uniformity of data collection, management of the collective rare diseases database, and data analysis.

Scientific Advisory Board (SAB). The NIH will establish an independent SAB to assist NIH in the evaluation of the Rare Diseases Clinical Research Network. The SAB will provide review of any new research activity that is developed in subsequent years of funding.

MECHANISM OF SUPPORT

This Request for Applications (RFA) will use NIH U54 award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. The anticipated award date is September 28, 2003.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm).

The NIH U54 is a cooperative agreement award mechanism in which the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award."

FUNDS AVAILABLE

The participating ICs intend to commit approximately $7.0 M in FY 2003 to fund 4 RDCRCs ($5 M) and 1 DTCC ($2 M) to new grants in response to this RFA. An applicant must request a project period of five years. Each RDCRC may request a budget for direct costs of up to $900,000 per year, but total cost may not exceed $1.25 M. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. It is anticipated that this RFA will be reissued in future years dependent on the availability of funds to the ORD.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic

Foreign institutions are not eligible to apply.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

These cooperative agreements (U54s) will require cooperation among the ORD Program Coordinator, NCRR Program Coordinator, the participating IC Program Officers, and Directors of the Rare Disease Clinical Research Centers, and the Director of the Data and Technology Coordinating Center to maximize their effectiveness. A number of issues need to be addressed in their applications including those highlighted in Organization of the Rare Diseases Clinical Research Network and below under Cooperative Agreement Terms and Conditions.

Cooperative Agreement Terms And Conditions Of Award

The following terms and conditions will be incorporated into the award statement and provided to the Principal Investigator as well as the institutional official at the time of award.

These special Terms of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR part 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements.

The administrative and funding instrument used for this program is the multiproject cooperative agreement (U54), an "assistance" mechanism rather than an "acquisition" mechanism, in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during the performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity.

Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the research will be shared among the awardees and the NIH Research Coordinators.

1. Awardee Rights and Responsibilities

Awardees will have primary responsibility for defining the details of the project within the guidelines of the RFA RR 03-008 and for performing the scientific activity, and agree to accept close coordination, cooperation, and participation of the NIH staff in those

aspects of the scientific and technical management of the project described below. Specifically, awardees have primary responsibility as described below.

RDCRC Director and the DTCC Director

The Rare Diseases Clinical Research Center Directors and Data and Technology Coordinating Center Director are the persons responsible for the overall management of their Centers and coordination with the other Centers. The relationship between the Clinical Centers and the Data and Technology Center should be one of equal partners in the Network. Each Center Director must devote at least 20% effort to this program.

Collaboration and Coordination

The collaboration of investigators between Centers is highly encouraged based on shared interests and complementary talents. The planned collaborating sites within the Center must be ongoing and active. Plans for evaluating and removing or replacing non-productive members of a Center consortium must be in place for each Center.

Steering Committee Membership and Meeting Attendance

Each Center Principal Investigator will be designated the Center Director. Each Center Director will be a voting member of the Network Steering Committee and participate in all Committee activities and decisions including, but not limited to, conference calls and special subcommittees as may be necessary. The Steering Committee shall be responsible for determining the frequency of meetings and scheduling the time and location. The Steering committee will establish the procedures for the function of the Centers network, as outlined in section "Steering Committee."

Data Coordination and Management and Sharing

The awardees will have primary rights to all data developed under these awards, subject to Government rights of access consistent with HHS and NIH policies. The DTCC will develop with the input of the Steering Committee a data management system. All Centers will place their data at the DTCC who will also offer analysis expertise for Network investigators. The intention of the NIH is that the data collected within this Network will be become a resource for the Rare Disease Community and will be made available to the scientific community. Criteria and mechanisms for data sharing among investigators within the Network and with the scientific community will be developed by the Steering Committee.

Publication and Presentation of Study Findings

Early publication of major findings is encouraged. Publications and oral presentations of work performed under this agreement will require appropriate acknowledgment of the Rare Disease Clinical Research Network and NIH support. The Steering Committee will establish the procedures

and criteria for presentation and publication of data developed within the Centers network.

Federally Mandated Regulatory Requirements

Each institution participating in the Rare Diseases Clinical Research Network is required to meet DHHS regulations for the protection of human subjects and FDA requirements for the conduct of research using investigational agents. At a minimum, these include:

o methods for assuring that each institution at which Rare Diseases Clinical Research Network investigators are conducting clinical studies has registered with the Office of Human Research Protections (OHRP; http://ohrp.osophs.dhhs.gov/) and has a Federalwide Assurance; that study protocols are reviewed and approved by the responsible Institutional Review Board (IRB) prior to patient entry; that active protocols are reviewed at least annually by the IRB, and that amendments are approved by the IRB.

- methods for assuring or documenting that each patient, or patient's parent/legal guardian, gives fully informed consent to participation in a research protocol prior to the initiation of the clinical study.

2. NIH Staff Responsibilities

One representative from ORD and one representative from the NCRR will be designated to serve as the Program Coordinators for this cooperative agreement. The ORD and NCRR Program Coordinators and one Program Officer from each participating IC will have substantial scientific/programmatic involvement during the conduct of this activity through technical assistance, advice and coordination above and beyond normal program stewardship for grants, as described below.

Steering Committee Membership and Meeting Attendance

The ORD and NCRR Program Coordinators and one Program Officer from each participating IC will serve on the Steering Committee and will participate in all Committee activities, including, but not limited to, meetings, conference calls, subcommittees, and special committees. They will assist in development of operating policies, quality control procedures, and policies that require cooperative action. However, while the ORD and the NCRR Program Coordinators and participating IC Program Officers will attend Steering Committee Meetings, their cumulative votes may never exceed 40 percent.

Monitoring Performance

The ORD and NCRR Program Coordinators and IC Program Officers will assist the Steering Committee in the development of procedures for monitoring the performance of the clinical studies. This includes participation in periodic on-site monitoring with respect

to compliance with protocol specifications, quality control and accuracy of data recording, and accrual. The NIH will also provide assistance to the DTCC in identifying technology resources, provide oversight of activities, including security and privacy issues.

Publication and Presentation of Clinical Studies Findings

The NIH staff may contribute, through review, comment, analysis, and/or co-authorship, to reporting results of the clinical studies and trials/studies to the investigator community and other interested scientific and lay organizations. Co-authorship by the NIH staff will be subject to approval in accordance with the NIH policies regarding staff authorship of publications resulting from extramural awards.

The Government, via the ORD Program Coordinator and the NCRR Program Coordinator, will have access to data generated under this Cooperative Agreement and may periodically review the data and progress reports. Information obtained from the data may be used by NIH staff for the preparation of internal reports on the activities of the clinical studies. However, awardees will retain custody of and have primary rights to all data developed under these awards.

Program Stewardship

The assigned Program Directors will be responsible for normal programmatic stewardship and monitoring of this award and approval of new pilot studies. The Program Directors may also serve as the NCRR Program Coordinator and the substantively involved IC Program officers. They may receive input and recommendations from other NIH staff in monitoring the awards.

3. Collaborative Responsibilities

All investigators within each Center and the Coordinating Center must be willing to work cooperatively and collaboratively both within their Center consortium and with other Centers. Each Center is expected to send two Center participants to three 2 day meetings in the first year to the Washington, D.C. area and biannually thereafter.

Steering Committee

A Steering Committee will be established to serve as the main governing body of the cooperative network. At a minimum, the Steering Committee will be composed of one representative from each of the RDCR Centers, one representative from the DTCC, the ORD Program Coordinator, the NCRR Program Coordinator, and other participating IC Program Officers. All members are expected to actively participate in all Steering Committee activities. The combined vote of NIH membership may never exceed 40 percent.

The Chairperson of the Steering Committee will be selected by the Steering Committee from among the non-Federal members during one of the early meetings of the Committee to be convened by the NIH Research Coordinators. All major decisions will be determined by the Steering Committee. The Committee will meet at least three times during the first 12 months of the program and at least semi-annually thereafter. As needed, the Steering Committee may establish subcommittees for special purposes. It is expected that most of the work of the Steering Committee will be performed in these subcommittees. All Centers must abide by decisions of the Steering Committee.

The Steering Committee will have responsibility for facilitating the conduct of the clinical studies, promoting trans-Center collaboration, establishing and updating the content of the web resource site, and establishing procedures for reporting results of Center studies. The NIH may provide additional funds in future years for new pilot projects. The Steering Committee should develop procedure for reviewing proposals for such projects. The Steering Committee will provide scientific and technical assistance and guidelines with respect to quality control, uniformity of data collection, management of the collective rare diseases database, and data analysis.

4. Arbitration

Any disagreement that may arise on scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to arbitration. An arbitration panel will be formed to review any scientific or programmatic issue that is significantly restricting progress. This panel will be composed of three members -- one selected by the Steering Committee or by the individual awardee in the event of an individual disagreement, a second member selected by the NIH, and a third member with expertise in the relevant area and selected by the two prior members. While the decisions of the Arbitration Panel are binding, these special arbitration procedures will in no way affect the awardee's right to appeal an adverse action in accordance with PHS regulations at 42 CFR Part 50, subpart D, and HHS regulations at 45 CFR Part 16.

PRE-APPLICATION MEETING

The ORD and NCRR anticipate holding a pre-application meeting in March 2003 to which all interested prospective applicants are invited. Program and review staff will make presentations that explain their goals and objectives for the Rare Diseases Clinical Research Network and answer questions from the attendees. A Grants Management Specialist will be available to answer financial questions. Prospective applicants are urged to monitor the NIH Guide Notice for the date and time of the meeting at http://grants.nih.gov/grants/guide/index.html. Additionally, consult the following website, established as an information resource for this RFA: http://rarediseases.info.nih.gov/news-reports/reports.html

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

- Direct your questions about scientific/research issues to:

Giovanna M. Spinella, M.D.
Office of Rare Diseases
National Institutes of Health
6100 Executive Blvd., Room 3B01 MSC 7518
Bethesda, MD 20892-7518
Telephone: (301) 402-4336
FAX: (301) 480-9655
Email: mailto:spinellag@od.nih.gov

or

Elaine Collier, M.D.
Division of Clinical Research
National Center for Research Resources
6705 Rockledge Drive, Room 6122 MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0794
FAX: (301) 480-3661
Email: mailto:CollierE@ncrr.nih.gov

- Direct your questions about peer review issues to:

Robert Weller, Ph.D.
Division of Clinical and Population Based Studies
Center for Scientific Review
6701 Rockledge Drive Room 3160
Rockville, MD 20892-7770
Telephone: (301) 435-0694
FAX: (301) 480-3962
Email: mailto:wellerr@csr.nih.gov

- Direct your questions about financial or grants management matters to:

Mary V. Niemiec
Lead Grants Management Specialist
Office of Grants Management
National Center for Research Resources
One Rockledge Centre, Room 6086

6705 Rockledge Drive MSC 7965
Bethesda, MD 20892-7965
Tel: (301) 435-0842
FAX: (301) 480-3777
email: mailto:mn20z@nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of the proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Giovanna M. Spinella, M.D.
Office of Rare Diseases
National Institutes of Health
6100 Executive Blvd., Room 3B01 MSC 7518
Bethesda, MD 20892-7518
Telephone: (301) 402-4336
FAX: (301) 480-9655
Email: mailto:spinellag@od.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.htmlin an interactive format. For further assistance contact GrantsInfo,
Telephone (301) 435-0714, Email: mailto:GrantsInfo@nih.gov

SUPPLEMENTAL INSTRUCTIONS

See additional application instructions under the sections RESEARCH OBJECTIVES and SPECIAL REQUIREMENTS.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and four signed, photocopies, in one package, including appendices to:

Center For Scientific Review
National Institutes Of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, one additional copy of the application must be sent to:

Elaine Collier, M.D.
Division of Clinical Research
National Center for Research Resources
6701 Democracy Boulevard, Suite 619, MSC 7965
Bethesda, MD 20892-4874

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes. While the investigator may still benefit from the previous review, the RFA application is not to state explicitly how.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the ORD and NCRR program coordinators.

Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Center for Scientific Review in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- Receive a written critique
- Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
- Receive a second level review by the appropriate National Advisory Council or Board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- Significance
- Approach
- Innovation
- Investigator
- Environment

The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Is the plan for training new investigators adequate and appropriate? For the DTCC, does the proposed approach incorporate scalable and secure technology?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? Are there novel methods for recruitment and outreach to health professionals?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? Are the investigators committed to collaborative and cooperative nature of this program?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support? Is there active participation of relevant patient support organizations?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL CONSIDERATIONS

DATA SHARING: The adequacy of the proposed plan to share data.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. Budgets must include funds for travel of the

Center Director to Bethesda, MD for a 2 day meeting three times in the first year, and semiannually in subsequent years.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: April 1, 2003
Application Receipt Date: April 29, 2003
Peer Review Date: July 2003
Council Review: September 2003
Earliest Anticipated Start Date: September 2003

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- Scientific merit (as determined by peer review)
- Availability of funds
- Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html);

a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN
SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://grants.nih.gov/grants/stem_cells.htmand at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html.

Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov/). It is the responsibility of the applicant to provide the official NIH identifier(s)for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any

portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.